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Early beta-blockade in severe traumatic brain injury (EBB-TBI)

Submission date
06/01/2021

Recruitment status
No longer recruiting

Registration date
07/01/2021

Overall study status
Completed

Last Edited
02/07/2024

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Damage to the brain following an accident has two forms. Primary injury happens at the moment of impact and cannot be altered. Secondary injury happens in the minutes, hours, and days after the event. It can be improved by medical treatment. Less secondary injury means patients are more likely to survive and more likely to survive with less disability.

One cause of secondary injury is adrenaline. Adrenaline is a hormone with many functions in the body. It is released in massive amounts at the time of the accident and remains high for days. Adrenaline supports blood pressure to help deliver oxygen to the brain, but the high levels damage the lining of blood vessels. This makes blood vessels leaky.

Fluid and cells leak from the bloodstream into the brain. This produces swelling and inflammation which reduces blood and oxygen supply to damaged areas of the brain. This leads to a vicious cycle of more swelling and inflammation. The result is secondary brain injury.

Blocking adrenaline may break the cycle. This is done with drugs called beta-blockers. Clinical databases suggest that patients taking or given beta-blockers do better after traumatic brain injury. The databases cannot say which beta-blocker is best, or how it should be given. Randomised trials are needed to see if beta-blockers do actually work.

Beta-blockers have side effects like reducing blood pressure that may be harmful. Before starting randomised trials it is essential to know that the drug and doses to be tested are safe for patients soon after brain injury. We aim to design a course of beta-blocker treatment that can be given to adults soon after having a serious head injury.

The study will use a beta-blocker called esmolol. Esmolol is quick to act and to wear off. It blocks the effects of adrenaline thought to be important in secondary injury to the brain. It is already used to control heart rate and blood pressure in patients during anaesthesia or in the intensive care unit.

In a previous study, esmolol was given to patients with shock from infection (sepsis). The patients with sepsis, like patients after a bad brain injury, were on a life support machine and

getting drugs to support blood pressure. Esmolol actually increased blood pressure and patients on esmolol were more likely to survive. This research is based on similar esmolol doses to the sepsis study.

At the end of the study, it is hoped that a safe protocol for beta-blocker treatment for patients soon after brain injury will have been established.

Who can participate?
Adults in the Intensive Care Unit after a severe traumatic brain injury.

What does the study involve?
During the study, participants will receive esmolol within 24 h of their injury to control heart rate. The first 6 patients will be given the same dose of the study drug, and after that, for each group of 3 patients, the study team will consider changing the doses of esmolol. Three sets of two additional blood samples, which are optional, will be taken during the period of receiving the study drug, and an additional electrocardiogram will be taken for each day of esmolol infusion. Apart from these measures, there are no additional invasive or non-invasive interventions required. Participants will be assessed for survival status, level of function, and quality of life at 6 months.

What are the possible benefits and risks of participating?
It is possible that beta-blockers reduce the overall damage after a severe traumatic brain injury, but it is not known if this is true, or if the drug and dose being used will be effective.

The main risk is low blood pressure that could reduce blood and oxygen supply to the brain. This could make overall brain damage worse. Drugs to support blood pressure are routinely given after severe traumatic brain injury.

Where is the study run from?
Southmead Hospital, Bristol (UK)

When is the study starting and how long is it expected to run for?
From October 2017 to April 2023

Who is funding the study?
The National Institute for Health Research (NIHR) Research for Patient Benefit Programme (UK)

Who is the main contact?
1. Dr Matt Thomas (Chief Investigator)
matt.thomas@nbt.nhs.uk
2. Dr Tony Timlin (Trial Manager)
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-003512-32

Integrated Research Application System (IRAS)
272010

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 44250, IRAS 272010

Study information

Scientific Title
Early intravenous beta-blockade with esmolol in adults with isolated severe traumatic brain injury: a Phase 2a intervention design study

Acronym
EBB-TBI

Study objectives
Beta-1 blockade after severe traumatic brain injury in adults reduces morbidity and mortality by reducing secondary brain injury driven by a hyperadrenergic state.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/07/2020, South Central – Hampshire A (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)207 104 8196; hampshirea.rec@hra.nhs.uk), ref: 20/SC/0219

Study design
Single centre non-randomised Phase 2a interventional study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Severe traumatic brain injury

Interventions
The primary objective of this study is a treatment schedule for esmolol. The starting point is a study of patients with sepsis who are receiving multi-organ support with ventilation and vasoactive drugs. Although adults after traumatic brain injury typically receive multi-organ support with ventilation and vasoactive drugs their responses may be different from patients with sepsis.

Thus this is an intervention design study using an adaptive dose-finding methodology (the continual reassessment method) to estimate the maximum tolerated dose of esmolol. That is the end point of the study is to find a dose schedule that combines the maximum possible effect in blocking the effects of adrenaline with the minimum possible toxicity. The effect will be judged according to the effect on heart rate, and the toxicity will be judged according to a failure to meet widely accepted brain perfusion pressure targets.

Participants will be recruited within 24 h using a deferred consent model as it is likely that the sooner neuroprotective interventions start, the greater the potential for benefit.

Esmolol infusion will start within 2 h of confirmation of eligibility using a personalised heart rate target for 96 h, plus a weaning phase to avoid rebound tachycardia, or until another stopping rule met.

All other treatments will be delivered according to established Intensive Care Unit guidelines based on internationally recognised principles. These are in accordance with the Brain Trauma Foundation guidelines. Heart rate is not a parameter that is targeted after brain injury, therefore the use of esmolol titrated to heart rate will not conflict with usual physiological goals. The use of other beta-blockers will not be permitted while receiving esmolol. After the intervention phase is completed, all treatments are at the discretion of the treating clinician.

Three sets of two additional blood samples will be taken in the intervention period, which are optional, and an additional electrocardiogram for each day of esmolol infusion. Apart from these measures, there are no additional invasive or non-invasive interventions required. ICU and hospital outcomes are routinely collected for national clinical audits. Follow up for survival status, level of function, and quality of life will occur at 6 months.

As this is primarily a dose-finding study, a modified continual reassessment method approach will be taken. The sample size and interim analyses are based on the requirement of this methodology. Up to 24 esmolol treated patients will be recruited and analysed in cohorts of three. Dose escalation will be considered after analysis of the first 6 patients, and every cohort of three thereafter based on the occurrence of dose-limiting toxicity.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
esmolol

Primary outcome(s)
Continual reassessment method derived maximum tolerated dose of esmolol that will achieve a ≥15% reduction of heart rate from baseline without compromise of cerebral perfusion pressure in adults within 24 h of severe traumatic brain injury will be assessed using both heart rate recorded by the bedside nurse using standard three-lead ECG monitoring, and cerebral perfusion pressure calculated as the difference between mean arterial pressure (measured via arterial catheter zeroed at the level of the tragus) and intracranial pressure (measured either by parenchymal monitor usually in the non-dominant frontal lobe or external ventricular drain), at 4 days and 6 months

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
30/04/2023

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Severe traumatic brain injury (Glasgow Coma Score of 8 or less after resuscitation or prior to intubation)
3. Within 24 h of injury
4. Intracranial pressure monitoring in situ

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
16

Key exclusion criteria
1. Life or limb-threatening extra-cranial injury (as determined by treating intensivist)
2. Admitted with perceived devastating brain injury for the purposes of prognostication or organ donation
3. Current participation in another clinical trial of an investigational medicinal product or within the preceding 30 days
4. Pregnancy
5. Breastfeeding
6. Hypersensitivity to beta-blockers
7. Cardiogenic shock
8. Decompensated heart failure (New York Heart Association class 4)
9. Untreated sick sinus syndrome or AV nodal conduction disorders including second or third-degree heart block
10. Untreated phaeochromocytoma
11. Acute severe bronchospasm secondary to asthma or chronic obstructive airways disease
12. Severe pulmonary hypertension (mean pulmonary artery pressure >55 mmHg)
13. Prinzmetal's angina
14. Severe metabolic acidosis (pH <7.1)
15. Use of verapamil within the preceding 48 h

Date of first enrolment
30/11/2020

Date of final enrolment
26/10/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

North Bristol NHS Trust
Southmead Hospital
Southmead Road
Westbury-on-trym
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BS10 5NB

Sponsor information

Organisation
North Bristol NHS Trust

ROR
https://ror.org/036x6gt55

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: PB-PG-0418-20029

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Current IPD sharing plan as of 10/06/2024:
The datasets generated during and/or analysed during the current study will be available upon request from Matt Thomas (matt.thomas@nbt.nhs.uk).
The type of data that will be shared: trial dataset as an Excel file, pseudonymised data.
Subject to GDPR and the Data Protection Act, for research use only, with no release of data into the public domain.
Please include the hypothesis you wish to test/reasons for the request in your application to the CI.

Previous IPD sharing plan:
The data-sharing plans for the current study are unknown and will be made available at a later date. It is expected that after publication the data will be made available to other researchers on request if approved by the Trial Management Group and Sponsor. Further details including contact name and email address will be provided at that time.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/06/2024	02/07/2024	Yes	No
Protocol article		12/06/2023	13/06/2023	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes